REMARKS/ARGUMENTS

The present amendment is submitted in accordance with the *Revised Amendment Format* as set forth in the Notice provided on the USPTO web site for the Office of Patent Legal Administration; Pre-OG Notices; signed 1/31/03.

Claims 1-6, 14-22, 24-26, 28, 30, 32 and 33 are pending in the application. No claims are allowed. Claims 1, 14, 19, 22 and 24 have been amended. Claims 7-13 and 25-31 have been canceled without prejudice to subsequent revival. Entry of the amendment, reconsideration of the rejection, and allowance of claims 1-6, 14-22, 24 and 32-33 are requested.

The Amendment

In order to expedite prosecution of the application, the claims have been amended. However, the amendment is made to advance the case toward allowance and should not be construed as an acquiescence in the rejection. No new matter was added by this amendment.

Claim 1 has been amended to clarify that the method includes additional steps as suggested by the Examiner. As such, claim 1 has been amended to include the following steps: "transferring the reconstructed zygote or oocyte into an oviduct of a recipient female of the same species as the zygote or oocyte"; allowing the reconstructed zygote or oocyte to develop to term "in the recipient female such that a hard shell egg is laid by said recipient female; and incubating the egg in order to hatch the transgenic chicken". Support for this amendment can be found on page 11, lines 9-15 and on page 35, lines 1-20 of the specification.

Claims 14 and 19 have been amended to specify that the reconstructed zygote or oocyte develops to term "in the recipient female such that a hard shell egg is laid by the recipient female; and the egg is then incubated in order to hatch the transgenic chicken". Support for this amendment can be found on page 11, lines 9-17 and on page 35, lines 1-20 of the specification.

Claims 22 and 24 have been amended to add "a comma" after reference to claim 21 and claim 14, respectively.

Claims 7-13 and 25-31 have been canceled.

Rejections under 35 U.S.C. §112

Claims 1-6, 14-22, 24-26, 28, 30, 32 and 33 are rejected under 35 U.S.C. §112 for allegedly lacking enablement. The Office Action maintains that the specification *fails to provide guidance or teachings* to show that cloned chicken could be produced by the claimed method of nuclear transfer. In particular, the Office Action notes that the specification teaches general methods of ovum transfer but does not provide teachings with regard to the generation of a cloned/transgenic chicken. The Examiner maintains that the *nuclear transfer art is unpredictable.*

To the extent that the rejection applies to the claims as amended, Applicants respectfully traverse the rejection.

MPEP 2164.01(a)[1] states the following:

> There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:
>
> (A) The breadth of the claims;
> (B) The nature of the invention;
> (C) The state of the prior art;
> (D) The level of one of ordinary skill;
> (E) The level of predictability in the art;
> (F) The amount of direction provided by the inventor;
> (G) The existence of working examples; and
> (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

MPEP 2164.01(a) also states:

> **It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others.** The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands,* 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407.

[1] MPEP 2164.01(a) Undue Experimentation Factors

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).
>
> The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. (Emphasis added.)

The Examiner indicates that the claims are not enabling because they fail to provide a step of transferring the resulting NT unit to a recipient hen of the same species; and that the only guidance provided in the specification is by transferring a reconstructed zygote or embryo to the oviduct of the recipient hen to produce a hard shell egg which can then be incubated to generate a cloned chick. The Office Action asserts that the claims, as written, are not enabling because they merely recite that the reconstructed zygote/oocyte is allowed to develop to term.

As shown above, independent claim 1 has been amended and now specifies that the reconstructed zygote or oocyte is transferred into an oviduct of a recipient female of the same species and is allowed to *develop to term in the recipient female* such that a hard shell egg is laid by the female. The egg is then incubated in order to hatch the transgenic chicken. Claims 2-6 depend on claim 1. Similarly, independent claims 14 and 19 have been amended to further specify that the reconstructed zygote or oocyte develops to term in the recipient female such that a hard egg is laid by the female, and the egg is incubated in order to hatch the cloned/transgenic chicken. Claims 15-18 and 24 depend on claim 14. Claims 20-22 depend directly or indirectly on claim 19. As indicated in the amendment section above, Applicants support these amendments in the specification and believe that the amended claims are now in condition for allowance.

Claim 32 is an independent claim that refers to *a method of preparing a recipient cell*. Claim 33 depends directly on claim 32. In order to address this rejection, Applicants respectfully request clarification as to why claims 32-33 are rejected under 35 U.S.C. §112, first paragraph.

I. The Amount of Guidance Provided in the Specification and The Existence of Working Examples

According to the Office Action, the specification provides guidance for the production of a reconstructed chicken zygote or oocyte, but fails to provide *an enabled use* for the chicken zygote or oocyte. Herein, the Examiner argues that the specification only teaches this use for the reconstructed chicken zygote or oocyte but fails to teach an enabled use for the claimed zygotes or oocytes; and that the generation of transgenic chickens and cloned chickens is not predictable.

The Examiner appears to assert that although Applicants have successfully produced a reconstructed zygote or oocyte they have not taught an enabled use for the same. The Examiner cites the lack of working examples in the specification and the general unpredictability in the art as further reasons why one skilled in the art would be required to engage in undue experimentation in order to make the claimed transgenic chicken.

But Applicants teach on page 35, by way of *example*, a step-by-step procedure of how the reconstructed zygote or oocyte can be transferred into a recipient hen and can thereby be developed to term within the recipient hen (see page 35 of the specification, lines 1-19). Specifically, the hen is anesthetized, surgically treated, and the donor ovum is gently applied to the open infundibulum (see page 35, line 12). The ovum is then allowed to move into the infundibulum and into the anterior magnum by gravity feed (line 13) after which the incision is closed (line 14). The laid eggs are collected and incubated in a Jamesway incubator (lines 18-19) and chicks hatch 21 days later. Hence, Applicants have taught an enabled use for the reconstructed zygote or oocyte by way of example.

II. The Level of Ordinary Skill in the Art

The courts have repeatedly held that a "patent need not teach, and preferably omits, what is well known in the art" *(Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Company et al.,* 221 USPQ 481 (Fed. Cir. 1984)).

Besides describing a form of ovum transfer in their own working example, the specification incorporates by reference Tanaka *et al.* (*Journal of Reproduction and Fertility,*

100:447-449, 1994) (see page 8 of the specification, lines 15-16). Tanaka *et al.* produced chicks by *in vitro* fertilization (IVF) by returning the fertilized ovum into the oviduct of recipient hens to complete the egg and shell formation. Tanaka *et al.* successfully hatched 6 live chicks from 12 fertile ova and 9 healthy chicks from ten control ova (after subsequent transfer to recipient hens) (see abstract). Thus, Tanaka *et al.* demonstrated in 1994 that fertile eggs can be obtained trough IVF of ova removed shortly after ovulation and subsequently transplanted into the oviduct of recipient hens (see Tanaka *et al.*, page 448, 2nd column, 3rd paragraph).

Further, the specification incorporates by reference Wilmut and Campell (GB 2332751B) who reported the production of reconstituted animal embryos via nuclear transfer of a diploid donor cell into a suitable recipient cell in 1996 (see page 3 of the specification, lines 8-15). Their invention was useful for the production of transgenic animals (see GB 2332751B abstract). As a result of their work, seven recipient ewes became pregnant (sheep) which resulted in the birth of five live lambs of which two died after birth and three survived (see GB 2332751B, page 29, lines 25-28).

The specification also cites several U.S. patents that teach how a nuclear donor cell is transfected with a vector construct that contains a transgene. Methods for transfection are known in the art and include retroviral vectors, retrotransposons, adenoviruses, adeno-associated viruses, naked DNA, lipid-mediated transfection, electroporation and direct injection into the nucleus. Such methods, particularly as applied to avians, are discussed in Bosselman (U.S. Patent No. 5,162,215), Etches (PCT WO99/10505), Hodgson (U.S. Patent No. 6,027,722), Hughes (U.S. Patent No. 4,997,763), Ivarie (PCT WO99/19472), MacArthur (PCT WO97/47739), Perry (U.S. Patent No. 5,011,780), Petitte (U.S. Patent Nos. 5,340,740 and 5,656,479), and Simkiss (PCT WO90/11355), all incorporated by reference in this application (see page 28 of the specification). For example, Bosselman *et al.* produced transgenic chickens whose cells contained and expressed a replication-defective retroviral vector nucleic acid sequence (see abstract). Their results demonstrated successful germline transfer of vector sequences. Of 5 G.sub.0 males that were bred (4 had been injected as embryos with an ME111 vector and 1 had been injected as an embryo with a SW272/cGH vector), all 5 males passed vector sequences on to a fraction of their offspring (G.sub.1). The percentage of these G.sub.1

(transgenic) offspring with vector sequences varied between 1% and approximately 8% (see Bosselman *et al.*, Example 4).

Thus, it is asserted that the prior art in combination with Applicants' teachings provide considerable direction and guidance of how to use the reconstructed zygote or oocyte in order to produce a transgenic/cloned chick. Applicants have attached copies of the above discussed references for the convenience of the Examiner.

III. The Level of Predictability in the Art and The Nature of the Invention

Since the prior art (*supra*) in combination with Applicants' teachings (*supra*) provide considerable direction and guidance of how to use the reconstructed zygote or oocyte in order to produce a transgenic/cloned chick, undue experimentation is not required. In fact, the quantity of experimentation that is necessary in order to practice the invention may be complex but not undue. It is respectfully indicated that complex experimentation does not equal undue experimentation. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (*In re Certain Limited -- Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A. B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

The Office Action indicates that the quantity of experimentation necessary to determine the parameters for nuclear transfer for the production of reconstructed chicken zygotes, oocytes or cloned or transgenic chickens, the alleged lack of working examples provided, and the unpredictable state of the art in nuclear transfer and transgenics, would require undue experimentation on the part of the skilled artisan. However, the Examiner does not provide a specific example of why the *quantity of experimentation* would be undue when practicing the instant invention other than citing general references with respect to the nuclear transfer art (see *Office Action* mailed on December 5, 2001). The Examiner cited Westhusin *et al.* (page 4) to show the unpredictable state of the art of nuclear transfer with regard to the unpredictable factors such as species difference, donor cells, and genetic modifications. However, Westhusin *et al.* discuss the state of the art of cloning cattle, sheep, goat, mice and pigs

in 2001. Westhusin *et al.* do not discuss the cloning of chicken. The Examiner cited Wall *et al.* (page 7) to illustrate that the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgenic construct; and the particular genetic elements required for appropriate expression vary from species to species. However, Wall *et al.* discuss transgenic livestock such as cattle, pigs, sheep as well as rabbits, mice and rats in 1996. Wall *et al.* do not discuss transgenic chicken. In fact, none of the references cited by the examiner specifically discuss nuclear transfer in chickens. On the other hand, Applicants have cited Bosselman and others who have sucessfully produced transgenic chickens via germline transfer (*supra*) as well as Wilmut and Campbell who were able to clone sheep (*supra*) via nuclear transfer. The references cited by Applicants in combination with the teachings of this invention challenge the idea that nuclear transfer is inherently unpredictable. In fact, if that were the case it would not have been possible to ever produce such advanced species as sheep via nuclear transfer. Notwithstanding that assertion, experimentation was still required to achieve that end. The same is true for the instant invention. As described in *Wands*, a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should precede." *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982).

In light of the foregoing amendment and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-6, 14-22, 24 and 32-33 under 35 U.S.C. §112.

Rejections under 35 U.S.C. §102

Claim 25 is rejected under 35 U.S.C. §102(a) as being allegedly anticipated by WO 00/11151 (Ivarie *et al.*), published March 2, 2000 and under 35 U.S.C. §102(b) as being allegedly anticipated by WO 99/19472 (Ivarie *et al.*), published April 22, 1999.

Claim 25 has been canceled without prejudice. Hence, the rejection is moot.

Claim 26 is rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Chang *et al.* (Cell Biology International, 21:495-499, 1997).

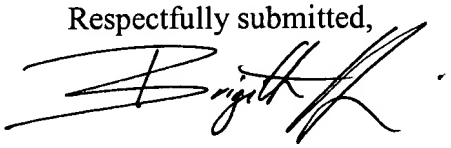
Claim 26 has been canceled without prejudice. Hence, the rejection is moot.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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